

Impact of a tailored oral vitamin D supplementation regimen on serum 25-hydroxyvitamin D levels in early breast cancer patients: a randomized phase III study[†]

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Received 15 December 2015; revised 7 March 2016; accepted 17 March 2016

Background: A minority of early breast cancer (EBC) patients treated with adjuvant or neoadjuvant chemotherapy have sufficient baseline vitamin D (vitD) level. This randomized phase III study assessed the safety and efficacy of a tailored, high-dose, oral vitD supplementation in restoring a normal 25-hydroxy vitD (25OHD) level in this population.

Patients and methods: Participants received a 6-month conventional (C) vitD and calcium supplementation or a 6-month high-dose oral vitD regimen tailored on the deficiency (T) and a conventional calcium supplementation. The primary end point was the 6-month percentage of 25OHD serum level normalization.

Results: A total of 215 patients including 197 patients with vitD deficiency were recruited, and 195 patients were randomized (T, 100; C, 95). Compliance to the daily oral supplementation was 68.4% and 67% in the C and T arms, respectively. Discontinuous high-dose vitD compliance appeared higher in the T arm (77%). At 6 months, more patients presented with a normalized vitD level in the T arm (30% versus 12.6%; $P = 0.003$). Supplementation was well tolerated, and no significant difference in the treatment-related toxicity between the two arms was reported. Fifty-two patients without vitD normalization from the C arm switched to the T arm after 6 months. At 12 months, 44% of these patients achieved vitD normalization.

Conclusion: A tailored high-dose oral vitD supplementation safely allows a higher percentage of the serum 25OHD level normalization compared with a conventional regimen in chemotherapy-treated EBC patients. As compliance to a daily oral supplementation remains poor in this setting, an adaptation of the treatment schedule is warranted.

Clinical trial number: NCT01480869.

Key words: early breast cancer, vitamin D, chemotherapy

introduction

Patients with early-stage (EBC) or locally advanced breast cancer are often treated with chemotherapy and anti-hormonal therapy [1]. Such therapies can lead to cancer treatment-induced bone loss, due to premature ovarian failure or direct cytotoxic effects of the chemotherapy, causing an increase in the skeletal morbidity risk [2–4]. Moreover, VitD insufficiency affects about 50% of women and even more patients with EBC [5–8]. This insufficiency worsens the multifactorial bone metabolism alterations

observed in these patients, increasing the osteoporosis risk [9], particularly in women with EBC [5–7]. VitD insufficiency may also contribute to the musculoskeletal pain induced by aromatase inhibitors, because of its role in the estrogen-related pathway [10]. These data are strongly consistent with the new concept of breast cancer etiology in which the contribution of vitD-dependent pathways should be taken into account.

Circulating 25-hydroxy vitD (25OHD) is considered as the best indicator of vitD body stores, providing an integrated measure of all vitD sources [11–13]. A minimum 25OHD blood level target of 30 ng/ml (75 nmol/l) is recommended. Below this value, patients suffer from mild (29–20 ng/ml), moderate (19–10 ng/ml) or severe vitD deficiency. As vitD deficiency is particularly common in these patients [5–8], current guidelines recommend daily supplementation with 1200 mg calcium and 400 IU vitD [14]. However, this seems insufficient. Indeed,

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[†]Presented in part at the 2013 and 2014 San Antonio Breast Cancer Symposiums.

Crew et al. reported that 1 year of daily 400 IU vitD3 supplementation allowed the normalization of the 25OHD serum values in less than 15% of the 74% premenopausal EBC patients with baseline vitD deficiency [5]. Similarly, a daily low-dose vitD supplementation failed to significantly increase the 25OHD level in breast cancer patients with vitD deficiency (<32 ng/ml) at baseline [15]. These patients were affected by a significantly lower lumbar bone mineral density (BMD). On the other hand, Khan et al. [10] showed that weekly 50 000 IU vitD3 supplementation was associated with a lower incidence of musculoskeletal pain. Thus, vitD deficiency in breast cancer patients does not seem to respond to standard low-dose vitD supplementation and might be linked to decreased BMD [15, 16]. Similarly, an international group of experts recently recommended that patients with breast cancer treated with aromatase inhibitors should receive daily vitD doses between 1000 and 5000 IU [17]. Correction of vitD deficiency in EBC patients appears crucial. The efficacy of a high-dose vitD supplementation remained to be validated in a randomized phase III study.

We report the safety and efficacy analysis of a tailored oral vitD supplementation regimen, using the schedule derived from the recommendations by Holick [18] and Cavalier [19], compared with a conventional regimen for restoring a normal 25OHD level in 195 deficient EBC patients treated with adjuvant or neoadjuvant chemotherapy.

patients and methods

study design

We designed a multicenter, open-label, randomized, phase III study comparing, on a 1:1 basis, an oral vitD supplementation regimen tailored on the baseline level of 25OHD deficiency [tailored (T) arm] with a conventional regimen [control (C) arm] in patients with vitD deficiency (<30 ng/ml). Patients were stratified according to three baseline vitD deficiency levels [<10 or $(10-20)$ or $(20-30)$ ng/ml], within 7–12 months after the first day of chemotherapy [stratification $(0-7)$ or $(7-12)$ months], hormone receptor positivity (yes or no) and menopausal status (peri- and premenopausal or menopausal). In the T arm, patients received 100 000 IU vitamin D3 on day 1, 15, 28, 43, 58 and at 3 months for baseline vitD deficiency levels <10 ng/ml, on day 1, 15, 28, 43 and at 3 months for levels $[10-20]$ ng/ml and on day 1, 15 and at 3 months for levels $[20-30]$ ng/ml (Figure 1). Patients in the C arm received daily 400 IU vitamin D3. Quality of life (QoL) was assessed as a secondary end point using the EORTC QoL Questionnaire Core 30 (EORTC QLQ-C30) v.3.

eligibility criteria

Female patients with histologically confirmed primary EBC, treated in the last 12 months with adjuvant or neoadjuvant chemotherapy, and with an ECOG performance status of <2 were enrolled into the study. Patients were excluded in case of known hypersensitivity reaction to vitD or calcium compounds, known comorbidities affecting the vitD/calcium balance or bone

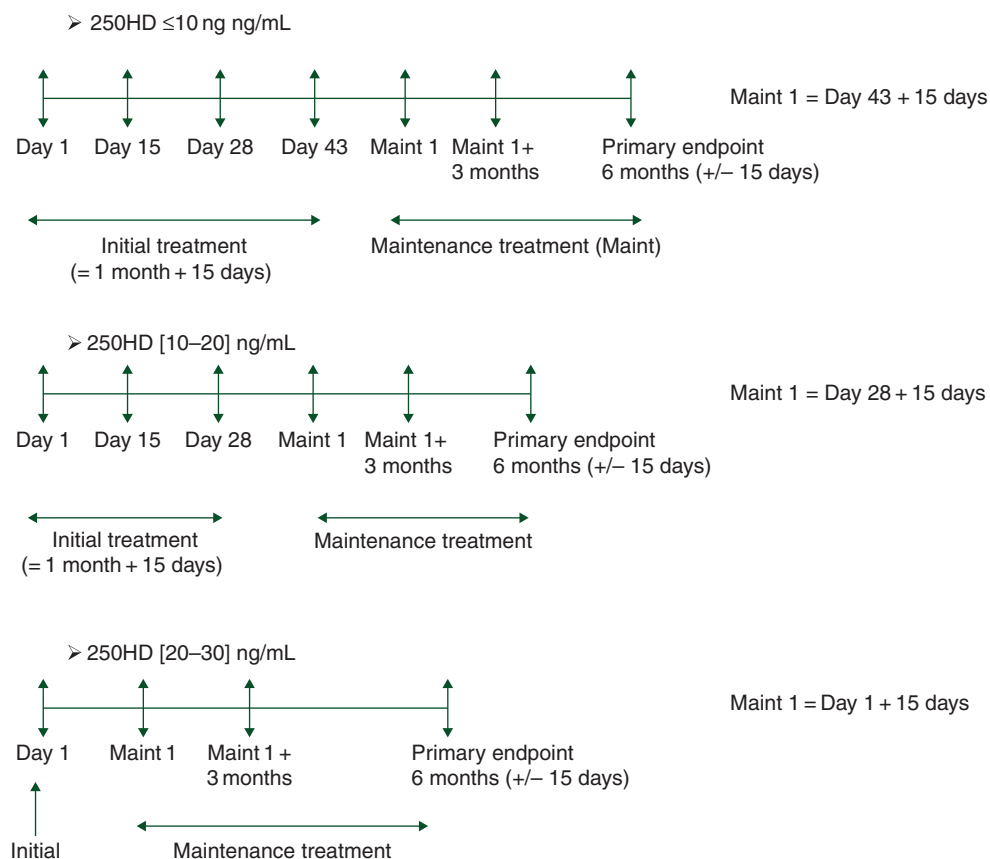


Figure 1. Tailored oral vitamin D was determined depending on the initial serum 25OHD levels as follows: patients had to take one oral dose of 100 000 IU vitD on the corresponding day (D). For subsequent maintenance (M), oral doses of 100 000 IU vitD were taken every 3 months, beginning 15 days after the last initial treatment dose.

health, concomitant vitD supplementation. Other exclusion criteria are described in supplementary Methods, available at *Annals of Oncology* online.

safety

Adverse events were graded according to the NCI CTCAE, v4.0. All patients who received one or more dose of drug were included in the safety analysis. Crossover to the T arm was allowed after 6 months of conventional treatment if the serum vitD level had not normalized. All patients gave written informed consent before the study. The protocol was approved by the local ethics committees and the study was conducted according to the international standards of good clinical practice.

assessment of outcomes

Samples for calcium and vitD serum levels were collected centrally at baseline and during follow-up. Biochemical analyses were carried out on a Cobas6000 automaton (Roche Diagnostics, France). VitD levels were measured using the DiaSorin 25-hydroxyvitamin D-¹²⁵I RIA kit (DiaSorin, France), which equally measures circulating 25OHD2 and 25OHD3 to provide total circulating 25OHD levels.

A 24-h urinary calcium dosage was performed in external biological laboratories the week before the follow-up visits, using local normal values. The 25OHD dosages were used for the primary end point assessment at 6 months.

quality-of-life assessment

Responses to the EORTC QLQ-C30 were transformed into 0–100 standardized scores, with a high score representing a high level of symptoms, functioning or a good QoL. Patients were asked to complete the questionnaire at baseline, and at 6, 12, 18 and 24 months.

end points and statistical analysis

The primary end point was the increase of normalization of serum 25OHD, defined as a 25OHD blood-level minimum target of 30 ng/ml, between the control and experimental arms from 20% to 45%, respectively. The secondary objectives were to evaluate the percentage by arm of patients with a normal vitD value at 12, 18 and 24 months, and the percentage of 25OHD serum normalization after 6 months of crossover in the C arm population. This article reports the safety, efficacy, QoL and crossover.

One hundred forty-four assessable patients were needed to establish the superiority of the experimental over the control arm with a 90% power. Considering that 10% of the randomized patients might not be assessable, 158 patients had to be included. The prevalence of vitD deficiency in the target population estimated at 60%, and it was necessary to select 264 patients. The complete statistical methods, including additional secondary end points, unplanned analysis and the compliant population definition are described in supplementary Methods, available at *Annals of Oncology* online.

results

patients' characteristics at baseline

The trial accrued 215 patients and randomized 195 patients, 100 and 95 patients in the T and C arms, respectively, from July 2011 to January 2013 in two French centers (Figure 2). Twenty patients were not randomized (18 without vitD deficiency, 1 treated with adjuvant chemotherapy more than 1 year before enrolment and 1 with baseline hypercalciuria) and were excluded from the analysis. All randomized patients were analyzed for efficacy, and 182 patients (93%) were evaluable for toxicity. Patients' characteristics at baseline and treatments received were well balanced,

including median weight and neoadjuvant/adjuvant chemotherapy (Table 1, Supplementary data, available at *Annals of Oncology* online).

At baseline, 90.7% of the patients had vitD deficiency, mild in 39.5%, moderate in 46% and severe in 5.1% of the cases [25OHD (29–20), (19–10) and <10 ng/ml, respectively]. Baseline vitD deficiency was significantly more frequent in postmenopausal patients (97% versus 87%; $P = 0.012$) and in HER2-positive patients (HER2+ 100%; HER2 – 89.7%; $P = 0.0048$). Considering the low frequency of normal baseline vitD levels ($n = 18$), we evaluated the variables associated with 25OHD levels >20 ng/ml and found a significant correlation with the pathological subtype (23.8% deficiency <20 in the lobular histology versus 55.2% in the ductal histology and other subtypes, $P = 0.01$).

treatment compliance and vitamin D normalization

Compliance to the supplementation was similar in both arms: 68.4% and 67% of the C and T arm patients took at least 80% of the planned daily oral calcium supplementation. Compliance to the tailored high-dose discontinuous vitD schedule appeared higher as 85.9% of the units were taken by the T arm patients, with 77% patients taking at least 80% of the planned units. The median baseline vitD level was 18.4 ng/ml (range 2.3–28.9) and 18.4 ng/ml (4.8–29.5) in the C and T arms, respectively (supplementary Figure S1, available at *Annals of Oncology* online). After 6 months, significantly more patients in the T arm had a normalized serum vitD level compared with the C arm patients (30% versus 12.6%; $P = 0.003$). The median 6 month-vitD level was 24.2 ng/ml (8.1–39.2) and 28.1 ng/ml (7.3–51.8) respectively in the C and T arms ($P < 0.001$). In the compliant population, a 6-month normalization was reported in 38.5% ($n = 30$) and 16% ($n = 12$) in the T and C arms, respectively (Figure 3). Percentages of correction depending on the randomization arm and the baseline degree of vitD deficiency are presented in Figure 4. Percentage of correction was significantly higher in the T arm for patients included during fall (28% versus 3%; $P = 0.006$), there was a trend in favor of T arm for patients included during winter (52% versus 28%; $P = 0.083$), while there was no significant difference for patients included in spring and summer.

safety

VitD and calcium supplementation was well tolerated, with no difference in the treatment-related toxicity between the two arms (no serum vitD levels higher than the normal range, one case of asymptomatic hypercalciuria in each arm).

crossover

Fifty-two patients without vitD normalization from the C arm switched to the T arm after 6 months. At 12 months, 44% of these patients ($n = 23$) showed vitD normalization. Median 6- and 12-month vitD levels were 23.9 ng/ml (8.1–29.6) and 28.6 ng/ml (16.3–53.0) respectively ($P < 0.001$; supplementary Figure S2, available at *Annals of Oncology* online).

quality of life

Baseline compliance was high with 94% and 96% of completed forms in the C and T arms, respectively. Compliance

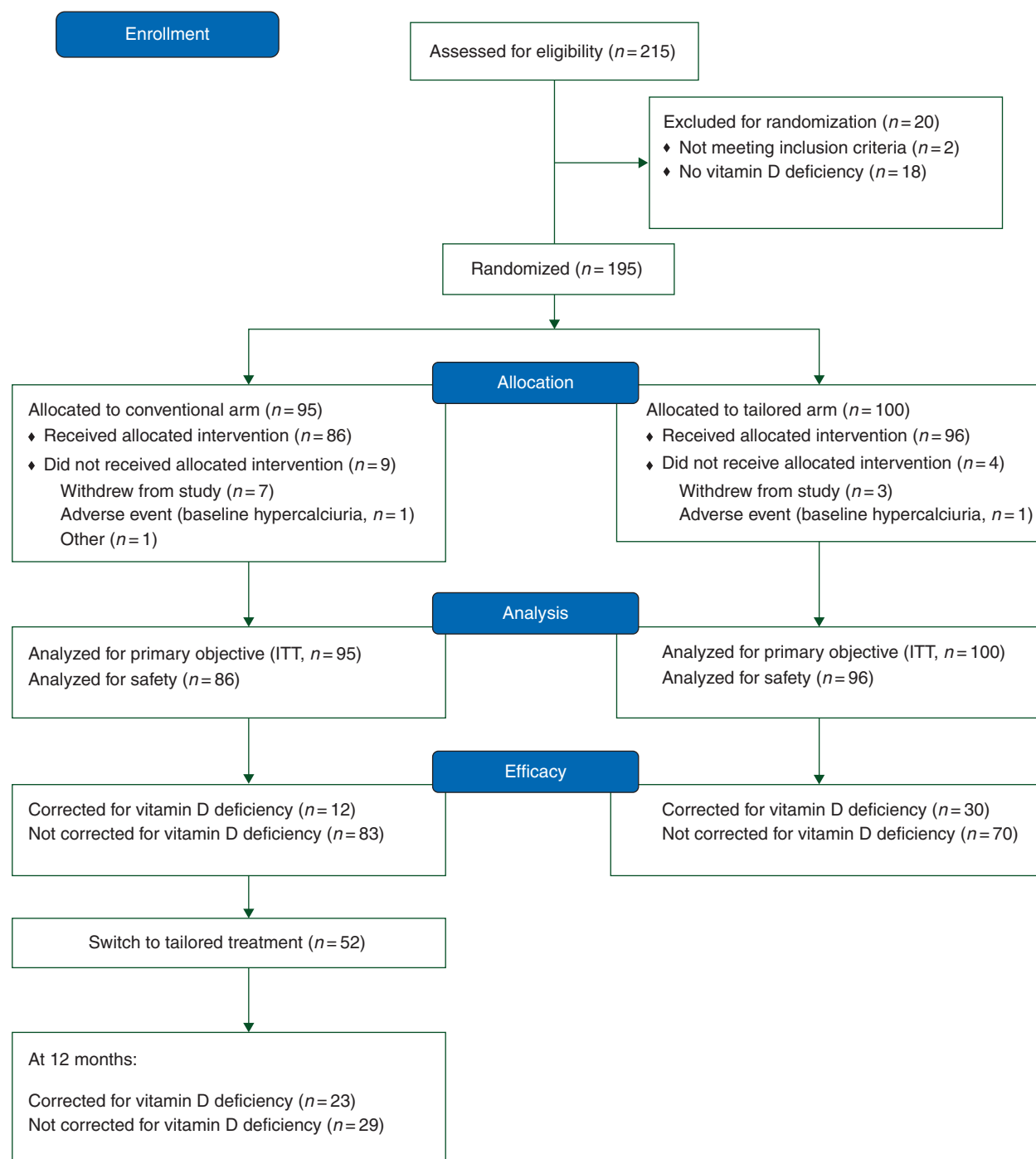


Figure 2. CONSORT Diagram of the study.

decreased over time in both arms (67 and 78 completed forms at 6 months) (supplementary Figure S3, available at *Annals of Oncology* online). There was no difference in baseline QoL, except for the physical function ($P=0.028$), higher in the experimental arm and diarrhea, more severe in the control group ($P=0.093$) (supplementary Table S1, available at *Annals of Oncology* online). No statistically significant difference was observed between treatment and control arms at 6 months. QoL worsened between baseline and 6 months in the T arm (supplementary Table S2, available at *Annals of*

Oncology online). The physical ($P<0.001$) and cognitive function ($P=0.005$) scores decreased, while fatigue ($P=0.022$), dyspnea ($P=0.016$) and diarrhea rose ($P=0.004$). The diarrhea symptom worsened between baseline and 6 months in the C arm ($P=0.026$). There was no significant difference in overall QoL between the normalized and deficient populations at 6 months. However, a deterioration of the QoL was observed in the normalized group in the physical ($P=0.006$) and cognitive functions ($P=0.002$), pain ($P=0.051$) and dyspnea ($P=0.014$) between baseline and after 6 months

Table 1. Patients' characteristics at baseline and delivered chemotherapy

	Tailored supplementation (N = 100)	Conventional supplementation (N = 95)
Median age (range)	51 (27–74)	49 (25–71)
Serum 25OHD level		
<10 ng/ml	7 (7%)	4 (4.2%)
10–19 ng/ml	49 (49%)	50 (52.6%)
20–29 ng/ml	44 (44%)	41 (43.2%)
Neoadjuvant or adjuvant chemotherapy		
Neoadjuvant	28 (28%)	31 (32.6%)
Adjuvant	72 (72%)	64 (67.4%)
Menopausal status		
Premenopausal	53 (53%)	52 (54.7%)
Postmenopausal	47 (47%)	43 (45.3%)
Hormone receptors' status		
HR positive	72 (72%)	67 (70.5%)
HR negative	28 (28%)	28 (29.5%)
Body weight (kg), median (range)	65 (45–105)	62 (45–133)
Body mass index, median (range)	19.7 (14.3–31.4)	19.2 (13.5–40.3)
Ethnical origin		
Caucasian	95	92
North African	5	3
Chemotherapy and targeted therapy		
FEC100—docetaxel 100 ^a	97	95
Docetaxel—cyclophosphamide	2	0
CMF ^a	1	0
Trastuzumab	5	7

^aFEC100—docetaxel 100: fluorouracil 500 mg/m², epirubicin 100 mg/m² and cyclophosphamide 500 mg/m² (FEC) i.v. on day 1 every 21 days for three cycles, followed by docetaxel 100 mg/m² i.v. on day 1 every 21 days for three cycles. Patients with HER-2 overexpressing tumors received also trastuzumab injections, beginning at the first docetaxel cycle. Patients presenting an allergic reaction to docetaxel received instead weekly paclitaxel (80 mg/m²) to complete the taxane treatment period. FEC100 premedication associated 8 mg of Ondansetron and 60 mg of methylprednisolone. To prevent docetaxel-related hypersensitivity or fluid retention, patients received premedication with six doses of corticosteroids—each equivalent to 50 mg of prednisolone—starting 12 h before and ending 18 h after the docetaxel infusion. CMF, cyclophosphamide, methotrexate, 5-fluorouracil; 25OHD: 25-hydroxy vitD.

(supplementary Table S3, available at *Annals of Oncology* online).

discussion

To our knowledge, we present here the first randomized, controlled trial evaluating the efficacy and safety of a high-dose vitD supplementation in EBC patients treated with adjuvant or neoadjuvant chemotherapy. We found a high prevalence (91.6%) of

baseline vitD deficiency, a value concordant with previous reports [5, 7, 8]. We evaluated two supplementation schedules to correct this deficiency. With a conventional supplementation (400 IU/D of vitD), 25OHD normalization was obtained in 12.6% of our conventional population. These results are similar to those reported by Crew et al. in their trial evaluating zoledronate [5].

We designed a tailored, higher dose, vitD schedule using discontinuous administration of 100 000 IU vitD vials to achieve a higher vitD normalization at 6 months. The rate of normalized serum vitD levels was more than doubled in the T arm when compared with that of the C arm. This strategy of dose increase was shown as feasible and safe in previous reports [10, 20, 21]. Indeed, a daily 1000 IU vitD supplementation could induce a 10 ng/ml vitD level increase, although a large multifactorial variability was reported [20]. Moreover, hypercalcaemia or hypercalciuria are rare and generally associated with 25OHD values over 150 ng/ml [22], values not reported in our trial (upper 25OHD value of 51.8 ng/ml in the T arm). Khan et al. [10] showed that weekly vitD uptakes of 50 000 IU appeared safe, in concordance with our results. Our tailored arm used supplementation doses equivalent to 6-month vitD daily intakes of 3279, 2732 and 1639 IU. A significantly higher proportion of patients achieved vitD normalization in the tailored arm (30% versus 12.6%; $P = 0.003$). These results compare favorably with two previous nonrandomized studies [10, 15]. Although our primary objective was met, more than two thirds of our population still suffered from vitD deficiency, leaving room for improvement. Surprisingly, we found a deterioration of QoL physical and cognitive functions, pain and dyspnea at 6 months. These results are in discrepancy with previous nonrandomized studies describing a decrease in joint pain in patients achieving vitD normalization [10, 23]. However, as 85% of our population was treated during their neoadjuvant/adjuvant chemotherapy, side effects could have burdened these results compared with previous studies evaluating patients under hormonal therapy, even though the two groups were well balanced regarding the treatments received. Daily sun exposure could induce heterogeneity in the results, as seen in the seasonal efficacy analysis. Another limitation of our study is the lack of concomitant evaluation of the daily diet vitamin D intake and the absence of self-compiled diary, which should be taken into account for further trials.

No difference in toxicity was detected between the two arms, raising the question of an additional increase in vitD dose intensity. However, particular attention must be paid to the compliance to daily oral supplementations in a context of adjuvant chemotherapy, taking into account the chemotherapy-induced emesis and high rate of noncompliance, 29% in our study. Future trials of dose-dense vitD supplementation should take into account the choice of optimized dose, timing and way of administration regarding these difficulties and should be encouraged considering the numerous biological and clinical impacts of vitD deficiency in EBC patients.

In conclusion, we found that an increase in vitD supplementation can achieve vitD normalization in one-third of the treated patients without significant side-effects. However, optimizations are still needed to increase compliance and optimize the delivered vitD dose to ensure optimal exposition of EBC survivors.

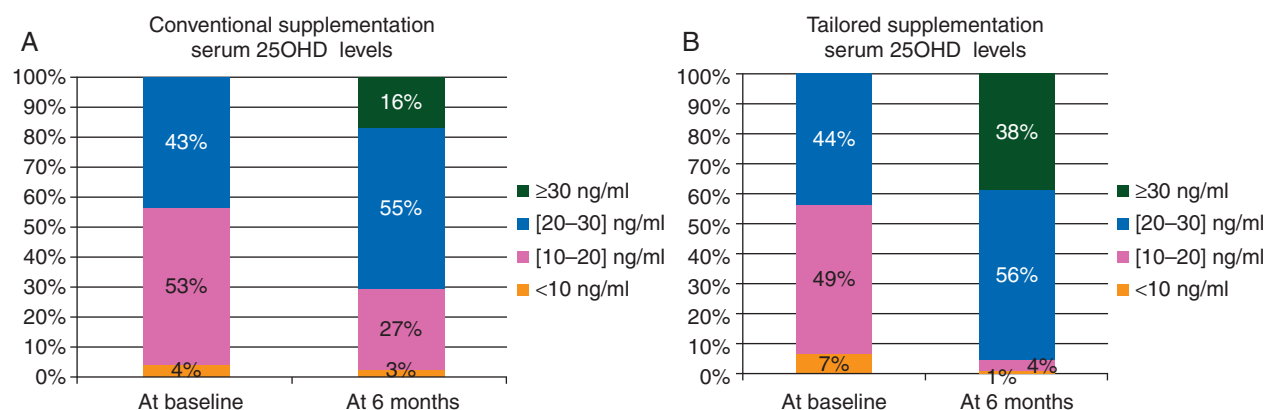


Figure 3. Baseline and 6-month 25OHD levels of patients in the compliant population. (A) Conventional arm. (B) Tailored arm.

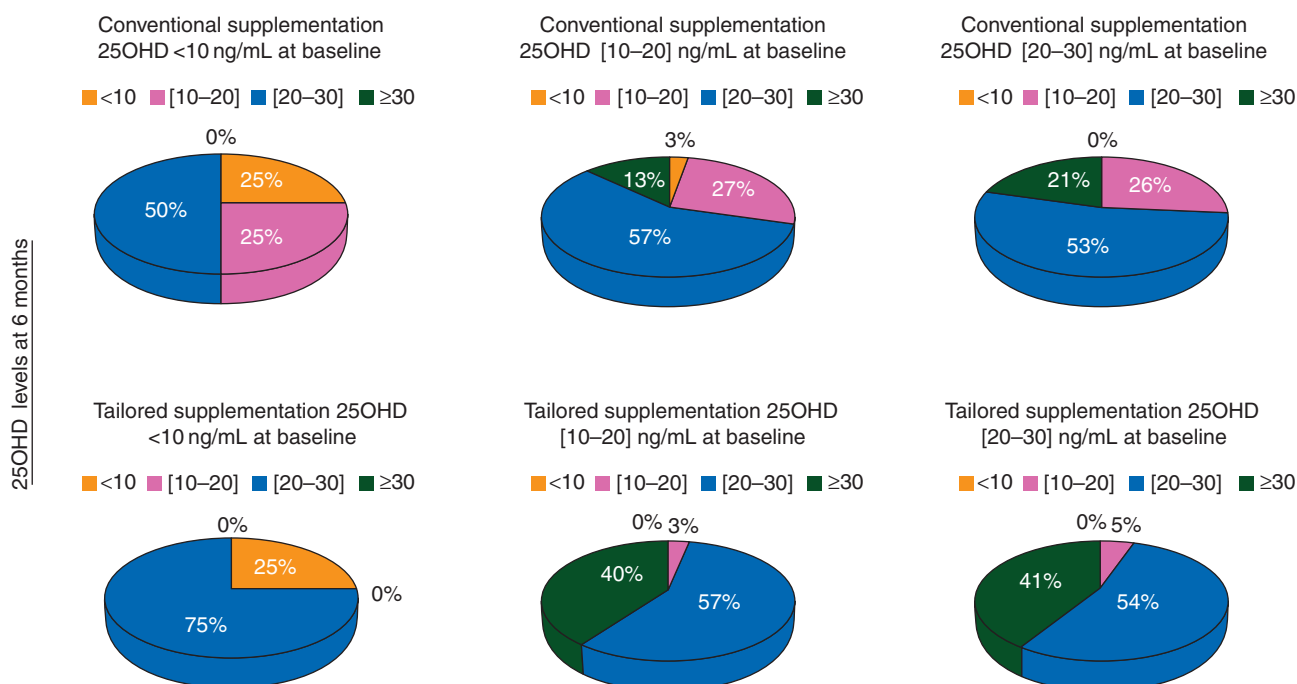


Figure 4. Distribution of serum 25OHD levels at 6 months depending on the treatment arm and on the baseline deficiency level.

acknowledgements

This study was supported by the Montpellier Cancer Institute (ICM), Montpellier, France. We thank Anne Suire, Clémence Carreira and Mélissa Luis for their work as clinical research assistants and data manager. We are grateful to Hélène de Forges for her assistance in editing the manuscript.

funding

There was no specific funding for this study.

disclosure

The authors have declared no conflicts of interest.

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Annals of Oncology 27: 1241–1248, 2016
doi:10.1093/annonc/mdw150
Published online 30 March 2016

Primary analysis of a prospective, randomized, single-blinded phase II trial evaluating the HER2 peptide AE37 vaccine in breast cancer patients to prevent recurrence

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Received 20 December 2015; revised 17 March 2016; accepted 19 March 2016

Background: AE37 is the li-Key hybrid of the MHC class II peptide, AE36 (HER2 aa:776–790). Phase I studies showed AE37 administered with granulocyte macrophage colony-stimulating factor (GM-CSF) to be safe and highly immunogenic. A prospective, randomized, multicenter phase II adjuvant trial was conducted to evaluate the vaccine's efficacy.

Methods: Clinically disease-free node-positive and high-risk node-negative breast cancer patients with tumors expressing any degree of HER2 [immunohistochemistry (IHC) 1–3+] were enrolled. Patients were randomized to AE37 + GM-CSF versus GM-CSF alone. Toxicity was monitored. Clinical recurrences were documented and disease-free survival (DFS) analyzed.

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